PROCESSES AND INTERMEDIATES FOR RESOLVING PIPERIDYL ACETAMIDE STEREOISOMERS

FIELD OF THE INVENTION

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This invention is directed to novel processes for resolution of piperidyl acetamide stereoisomers. The invention additionally is directed to synthetic intermediates and reaction products useful in such processes.

BACKGROUND OF THE INVENTION

Substituted piperidines have found use in the treatment of many nervous system disorders. For example, methylphenidate has been used to treat Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD) and cognitive decline in Acquired Immunodeficiency Syndrome (AIDS) and AIDS Related Complex (ARC) patients. (*See, e.g.*, Greenhill, *Child & Adol. Psych. Clin. N.A.*, **1995**, *4*, 123, and Brown, *Intl. J. Psychl. Med.*, **1995**, *25*, 21).

Many currently available synthetic routes to methylphenidate and other substituted piperidines involve preparation of racemic mixtures. (*See, e.g.,* U.S. Patent 2,507,631, to

Hartmann, *et al.*, and U.S. Patent 2,957,880, to Rometsch, *et al.*). There are, however, a number of disadvantages associated with racemic mixtures of such drugs. Current administration of racemic methylphenidate often results in notable side effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

U.S. Patent Nos. 2,507,631 and 2,957,880 disclose synthetic procedures wherein methylphenidate, alternatively known as methyl α-piperid-2-ylphenylacetate, is prepared through a multi-step process in which 2-chloropyridine and phenylacetonitrile initially are coupled to form α-pyrid-2-ylphenylacetonitrile. The resulting α-pyrid-2-ylphenylacetonitrile then is hydrated in the presence of acid to yield α-pyrid-2-ylphenylacetamide which, in turn, is either: (a) catalytically hydrogenated to yield α-piperid-2-ylphenylacetamide and then converted to methyl α-piperid-2-ylphenylacetate, or (b) converted to methyl α-pyrid-2-ylphenylacetate which, in turn, is hydrogenated to yield methyl α-piperid-2-ylphenylacetate.

In the first embodiment of U.S. Patent No. 2,507,631 and in the process described in U.S. Patent No. 2,957,880, α-piperid-2-ylphenylacetamide is first separated into the *threo* and *erythro* diastereomeric racemates. This is accomplished through evaporation of the solvent utilized in the hydrogenation (*i.e.*, acetic acid), addition of sodium hydroxide to precipitate the α-piperid-2-ylphenylacetamide free base, recrystallization of this amide from ethyl acetate, and preferential crystallization of the *erythro* form by passing gaseous hydrogen chloride through an ethanolic solution of the amide.

The isolated *erythro* racemate then is resolved through formation of the *l*-tartrate salt, repeated recrystallizations of this salt from 96% ethanol are performed until a constant rotation is obtained, and the *l-erythro* form of α-piperid-2-ylphenylacetamide is precipitated

with sodium hydroxide. The *l-erythro* form of α-piperid-2-ylphenylacetamide thus obtained is said to be subjected to epimerization to yield the desired *d-threo* diastereomer of α-piperid-2-ylphenylacetamide through treatment with 6 M potassium hydroxide. According to the disclosed procedure, the α-piperid-2-ylphenylacetamide thus obtained is converted to *d-threo* methyl α-piperid-2-ylphenylacetate through hydrolysis and esterification.

Some in the art have raised doubts as to whether the procedures disclosed in U.S. Patent Nos. 2,507,631 and 2,957,880 do, in fact, produce the desired *d-threo* isomer. Indeed, J.R. Soares, "Stereochemical Studies On Potential Central Nervous System Active Agents and Studies On The Chemistry Of Some 3-Benzoylpiperidines," 1971, Columbia University Ph.D. dissertation, p. 115, discloses that "all attempts to epimerize the resolved *erythro*-amides to the corresponding threo-amides by the procedure outlined in [U.S. 2,957,880] failed completely."

In any event, the synthetic procedure described in U.S. Patent Nos. 2,507,631 and 2,957,880 is wasteful in that it involves discarding the *threo* α-piperid-2-ylphenylacetamide racemate which is isolated following the recrystallization step and which typically represents approximately 25% of the acetamide product obtained via hydrogenation.

Consequently, there remains a need in the art for alternative synthetic procedures for the preparation of methylphenidate and other substituted piperidines. In particular, there is a need for synthetic procedures that do not require separating and discarding *threo* stereoisomers from the hydrogenation reaction product.

OBJECTS OF THE INVENTION

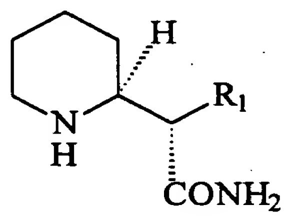
It is an object of the present invention to provide processes for the preparation of substituted piperidines.

It is another object of this invention to provide processes that provide synthetic intermediates and, hence, products having high optical purity.

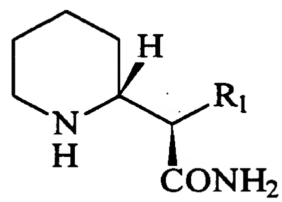
It is yet another object to provide processes that proceed more efficiently than the processes disclosed by the prior art.

SUMMARY OF THE INVENTION

These and other objects are satisfied by the present invention, which provides processes and intermediates for preparing piperidyl acetamides. In preferred embodiments, the processes of the invention comprise reacting *d,l-threo* piperidyl acetamide stereoisomers having formulas IIa and IIb:



IIa
l-threo

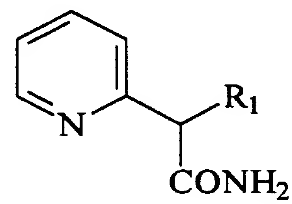


IIb
d-threo

(R_1 = aryl having about 6 to about 28 carbon atoms) with an acid resolving agent in an organic solvent, thereby forming acid salts of the *d-threo* stereoisomers preferentially with respect to the *l-threo* stereoisomers. The resulting acid salts then are reacted with aqueous base to form the corresponding piperidyl acetamide, which subsequently is converted to a corresponding ester.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides novel processes for stereoselective synthesis of a variety 2-substituted piperidine stereoisomers. In one aspect, the invention is directed to synthetic methods involving hydrogenation of pyridines having formula I:

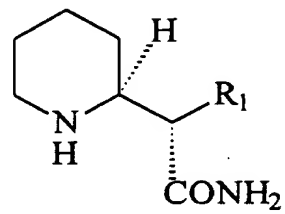


I

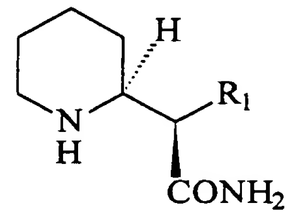
wherein R_1 is aryl having about 6 to about 28 carbon atoms. Aryl groups, as used herein, are aromatic groups containing a delocalized π-electron cloud. Such aromatic groups can be substituted with one or more substituents, such as, for example, halo, alkyl, aryl, hydroxy, alkoxy, carboxy, and cycloalkyl. Exemplary aryl groups include phenyl, naphthyl, xylyl, chlorophenyl, fluorophenyl, trifluoromethylphenyl, and bromophenyl. Phenyl groups are preferred.

This hydrogenation can be effected by any of the numerous techniques known in the art. One preferred hydrogenation technique involves reacting the pyridine with hydrogen gas in the presence of a suitable catalyst in an alkanoic acid having 1 to about 10 carbon atoms. The hydrogenation preferably run at 25 °C and 40 psi. Representative catalysts contain platinum, with platinum oxide being particularly preferred. One preferred alkanoic acid is acetic acid.

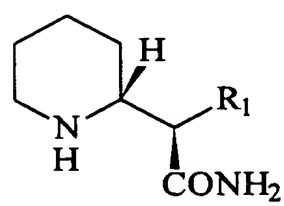
Hydrogenation of pyridine I provides a mixture of piperidine diastereomers IIa-d:



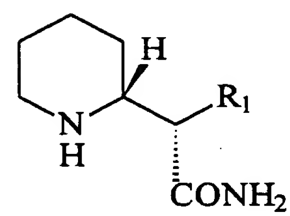
IIa
l-threo



IIc
d-erythro



IIb
d-threo



IId
l-erythro

In accordance with the present invention, this mixture is treated with an organic base in an organic solvent to epimerize the *erythro* stereoisomers into *threo* forms. The epimerization can, for example, be effected in an aromatic hydrocarbon solvent such as toluene using an alkali metal alkoxide such as potassium *tert*-butoxide. In preferred embodiments, the epimerization is effected at 70 °C in an aromatic hydrocarbon solvent such as toluene using two equivalents of an alkali metal alkoxide such as potassium *tert*-butoxide.

The resulting composition, which should consist predominantly of *d,l-threo* piperidyl acetamide stereoisomers, is reacted with an acid resolving agent in an organic solvent, thereby forming acid salts of the *d-threo* stereoisomers preferentially with respect to the *l-threo* stereoisomers. Alkyl groups according to the invention are hydrocarbons which are straight, branched, or cyclic. Such hydrocarbons can be substituted with one or more substituents, such as, for example, halo, hydroxy, alkoxy, and carboxy groups. Exemplary alkyl groups

include methyl, ethyl, isopropyl, *n*-butyl, *t*-butyl, n-pentyl, acetyl, trifluoromethyl, chloromethyl, and hexyl groups. Representative solvents include alcohols, alkyl alkanoates (*e.g.*, ethyl acetate), ketones (*e.g.*, acetone), and ethers (*e.g.*, tetrahydrofuran, dioxane). Preferred solvents are alcohols having 1 to about 5 carbon atoms, include branched and straight chain compounds such as ethyl, propyl and *tert*-butyl alcohol, with isopropanol being particularly preferred. The reaction of piperidyl acetamide stereoisomers with acid resolving agents preferably is performed with stirring at room temperature.

Representative acid resolving agents include L-(+)- or D-(-)- tartaric acid, dipivaloyl-D-tartaric acid, (1S)-(+)-10-camphorsulphonic acid, L-(-)-malic acid, (S)-(+)-mandelic acid, N-acetyl-*l*-aspartic acid (and other N-protected amino acids), (R)-(+)-1,1'-bi-s-napthol, (+)-camphoric acid, D-glucuronic acid, and derivatives thereof. Those believed to be useful for forming *d-threo* stereoisomers preferentially with respect to *l-threo* isomers include (+)-dibenzoyl-D-tartaric acid. Derivatives of D-(-)-tartaric acid are preferred, including those having formula (III):

$$HO_2CCH[OC(O)R_3]CH[OC(O)R_3]CO_2H \qquad \text{(III)}$$

where each R_3, independently, is aryl having 6 to about 28 carbon atoms or aralkyl having 7 to about 28 carbon atoms. Aralkyl groups according to the invention are those (such as, for example, benzyl groups, which both aryl and alkyl portions and are covalently bound to a core molecule (such as the above-noted carbonyl-functionalized tartaric acid) through the alkyl portions thereof.

In certain alternative embodiments of the invention, the piperidyl acetamide stereoisomers having formulas IIa and IIb are reacted with an acid resolving agent in an organic solvent to form acid salts of the *l-threo* stereoisomers preferentially with respect to the *d-threo* stereoisomers. Resolving agents believed to be useful for forming *l-threo*

stereoisomers preferentially with respect to *d-threo* isomers include (-)-dibenzoyl-L-tartaric acid. Derivatives of L-(-)-tartaric acid are preferred, including those having formula (III). Crystallization preferably is performed at ambient temperature.

The acid salts obtained via resolution typically are dissolved in water and treated with an aqueous base such as a carbonate, bicarbonate, or hydroxide to precipitate the corresponding piperidyl amide free base in substantially pure form. They then can be reacted with an alcohol having, for example, 1 to about 5 carbon atoms in the presence of acid to form the corresponding ester.

Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are not intended to be limiting.

Example 1

Preparation of *d-Threo*-methylphenidate Hydrochloride *Via* Diastereomeric Separation and Resolution of *d,l-erythro*-Amide (Comparative Example)

A. α-Phenyl-α-pyridyl-(2)-acetonitrile

Materials:

2-Chloropyridine (99%)	286 g (2.50 moles)
Benzyl cyanide (98%)	314 g (2.62 moles)
Sodium amide (90%)	217 g (5.00 moles)
Toluene	0.98 + 0.17 L
Water	0.87 L
Ethyl acetate	0.43 L
Hexanes	1.56 + 1.95 L
Brine	0.43 L

Procedure:

A 5L multi-neck glass reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.98 L). Sodium amide powder was added over a 1h period via a solid-addition funnel, keeping the reaction temperature below 30°C. The reaction mixture was stirred for 16h at ambient temperature. The reaction was then cooled to ~ 10°C, and quenched with 0.87 L water. Ethyl acetate (0.43 L) was added to solubilize the precipitated product. The organic layer was separated and washed once with 0.43 L brine. Solvent was removed from the organic layer on a rotovap, and toluene (0.17L), followed by hexanes (1.56 L), were added to the resulting residue. The resulting slurry was filtered. The filter cake was washed with hexanes (1.95 L), and dried to give 441 g of α-phenyl-α-pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

B. α-Phenyl-α-pyridyl-(2)-acetamide

Materials:

α-Phenyl-α-pyridyl-(2)-acetonitrile	441 g	(2.27 moles)
Conc. H_2SO_4	0.55 L	
Water	1.63 L	
50% NaOH	1.27 L	

Procedure:

The reactor was charged with conc. H_2SO_4, and cooled to ~ 10°C. α-Phenyl-α-pyridyl-(2)-acetonitrile (from Example 1.A) was added portionwise, keeping the temperature below 30°C. The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C, at which point water was added. The NaOH then was added to a pH of 12, keeping the temperature below 30°C. The resulting crystals were filtered, and the filter cake was washed with water and dried under vacuum to give 482 g (100%) of α-phenyl-α-pyridyl-(2)-acetamide.

NH_4OH can be substituted for NaOH to adjust the pH to 12. One advantage of using NH_4OH is that the by-product that is formed (ammonium sulfate) is more soluble in water then the by-product (sodium sulfate) formed when NaOH is used as the base. Thus, the product crystals are less likely to be contaminated with inorganic salts.

C. *d,l-erythro*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

α-Phenyl-α-pyridyl-(2)-acetamide	482 g (2.27 moles)
Platinum oxide (PtO_2)	8.06 g
Acetic acid	1.68 + 4.13 L
Celite	500 + 250 g
Ethyl acetate	3.10 + 0.62 + 2.07 + 2.07 + 4.13 + 0.21 L
Water	4.13 + 1.03 + 2.07 L
50% NaOH	0.56 L

Procedure:

The reactor was charged with α-phenyl-α-pyridyl-(2)-acetamide (from Example 1.B), acetic acid (1.68 L), and PtO_2. The reactor then was filled with hydrogen gas, and pressurized to 60 psi. The reaction mixture was hydrogenated at room temperature for 16h. The reaction mixture was filtered through a pad of Celite (500 g) to remove catalyst, and the Celite pad washed with acetic acid (4.13 L). The filtrate was concentrated under reduced pressure. Ethyl acetate (3.10 L) was added to the residue and stirred for 2h. The resulting crystals (first crop) were filtered, washed with ethyl acetate (0.62 L), and dried. The filtrate was concentrated under reduced pressure. Ethyl acetate (2.07 L) was added to the residue and stirred for 2h. The resulting crystals (second crop) were filtered, washed with ethyl acetate (2.07 L), and dried. The crystals from first and second crops were combined and dissolved in water (4.13 L), filtered through a pad of Celite (250 g), and the Celite pad was washed with water (1.03 L). The resulting filtrate was cooled to 10°C, followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The

crystals were filtered, washed with water (2.07 L), and dried to give 297 g (60%) of *d,l*--*erythro*-α-phenyl-α-piperidyl-(2)-acetamide.

D. *l-erythro*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

d,l-erythro-α-phenyl-α piperidyl-(2) -acetamide	297.2 g (1.361 moles)
D-(-)-Tartaric acid	204.3 g (1.361 moles)
Methanol	7.13 + 7.13 L
Water	2.0 L
50% NaOH	0.1 L

Procedure:

D-(-)-Tartaric acid dissolved in methanol (7.13 L) was added to a stirred solution of *d,l-erythro*-α-phenyl-d-piperidyl-(2)-acetamide (from Example 1.C), dissolved in methanol (7.13 L). The resulting clear solution was stirred for 16h, whereby the tartrate salt of *l-erythro*-acetamide crystallized out. The crystals were filtered, washed with methanol and dried. This tartrate salt was dissolved in water and 50% NaOH was added to a pH of 12, whereby the free base precipitated out. The precipitated crystals were filtered, washed with water and dried to give 119 *g* (40%) of *l-erythro*-α-phenyl-α-piperidyl-(2)-acetamide.

E. *d-threo*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

l-erythro-α-phenyl-α-piperidyl-(2)-acetamide	119g (0.544 moles)
Potassium t-butoxide (95%)	141.5g (1.198 moles)
Toluene	3.57L
Water	0.60 + 0.30 + 1.20L
Conc. HCl	0..24 + 0.12L
50% NaOH	0.14L

Procedure:

A mixture of 1-erythro-α-phenyl-α-piperidyl-(2)- acetamide (from Example 1.D), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (0.60L). Conc. HCl (0.24L) was added to this resulting mixture, and stirred for 0.5 h. The layers were separated, and the top organic layer was washed with a prepared solution of conc. HCl (0.12L) and water (0.30L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12, whereby the free base precipitated out. The crystals were filtered, washed with water (1.20L), and dried to give 101 g (85%) of *d-threo*-α-phenyl-α-piperidyl-(2)-acetamide.

F. *d-threo*-Methylphenidate Hydrochloride

Materials:

d-threo-α-phenyl-α-piperidyl-(2)- acetamide	101 g (0.46 moles)
Conc. H_2SO_4	121 mL
Methanol	1.1 L
Water	0.81 L
50% NaOH	175 mL
Diethyl ether	1.0 + 1.0 + 1.0 + 1.0 L
Magnesium sulfate	20 g
HCl gas	As needed.

Procedure:

A solution of *d-threo*-α-phenyl-α-piperidyl-(2)-acetamide (from Example 1.E) and conc. H_2SO_4 in methanol was heated to reflux and stirred for 2 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (0.81 L) and ether (1.0 L) were added to the residue. NaOH was added to a pH of 12, and the layers were separated. The aqueous layer was extracted with ether (1.0 L). $MgSO_4$ was added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas was passed

through the filtrate with stirring, whereby white crystals of *d-threo*-methylphenidate hydrochloride precipitated out. The crystals were filtered, washed with ether (1.0 L), and dried to give 100 g (80%) of *d-threo*-methylphenidate hydrochloride.

The overall yield for Example 1 was 14.7%.

Example 2

Preparation of *d-Threo*-methylphenidate Hydrochloride *Via* Epimerization and Resolution of *d,l-Threo*-amide Enantiomers

A. α-Phenyl-α-pyridyl-2-acetonitrile

Materials:

2-Chloropyridine (99%)	172 g (1.50 moles)
Benzyl cyanide (98%)	188 g (1.576 moles)
Sodium amide (90%)	130 g (3.00 moles)
Toluene	0.59 + 0.10 L
Water	0.52 L
Ethyl acetate	0.26 L
Hexanes	0.94 + 1.17 L
Brine	0.26 L

Procedure:

The reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.59 L). Sodium amide powder was added over a lh period via a solid-addition funnel, keeping the reaction temperature below 300°C. The reaction mixture was stirred for 16h at ambient temperature. The reaction was cooled to ~ 10°C, and quenched with 0.52 L water. Ethyl acetate (0.26 L) was added to solubilize the precipitated product.

The organic layer was separated and washed once with 0.26 L brine, and solvent was removed from the organic layer on a rotovap. Toluene (0. 10 L), followed by hexanes (0.94 L) were added to the resulting residue. The resulting slurry was filtered, and the

filter cake was washed with hexanes (1.17 L), and dried to give 265 g of α-phenyl-α-pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

B. α-Phenyl-α-pyridyl-(2)-acetamide

Materials:

α-Phenyl-α-pyridyl-(2)-acetonitrile	264 g (1.362 moles)
Conc. H_2SO_4	0.33 L (6.226 moles)
Water	0.98 L
50% NaOH	0.77 L

Procedure:

The reactor was charged with conc. H_2SO_4, and cooled to ~ 10°C. α-Phenyl-α-pyridyl-(2)-acetonitrile (from Example 2.A) was added portionwise, keeping the temperature below 30°C. The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C, the water was added, and the NaOH was added to a pH of 12, keeping the temperature below 30°C. The resulting crystals were filtered, the filter cake was washed with water, and dried under vacuum to give 289 g (100%) of α-phenyl-α-pyridyl-(2)-acetamide.

C. *d,l-erythro/threo*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

α-Phenyl-α-pyridyl-(2)-acetamide	289 g (1.365 moles)
Platinum oxide (PtO_2)	4.84 g
Acetic acid	1.01 + 2.48 L
Celite	300 + 150 g
Water	2.48 + 0.62 + 1.24 L
50% NaOH	0.33 L

Procedure:

The reactor was charged with α-phenyl-α-pyridyl-(2)-acetamide (from Example 2.B), acetic acid (1.01 L), and PtO_2. The reactor then was filled with hydrogen gas, pressurized to 60 psi, and the mixture hydrogenated at room temperature for 16h. The

reaction mixture then was filtered through a pad of Celite (300 g) to remove the catalyst, and the Celite pad is washed with acetic acid (2.48 L). The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in water (2.48 L), filtered through a pad of Celite (150 g), and the Celite pad was washed with water (0.62 L). The resulting filtrate was cooled to 10°C, followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The crystals were filtered, washed with water (1.24 L), and dried to give 297 g (100%) of a 4:1 mixture of *d,l-erythro*-α-phenyl-α-piperidyl-(2)-acetamide and *d,l-threo*-α-phenyl-α-piperidyl-(2)-acetamide.

D. *d,l-threo*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

Mixture of *d,l-erythro*-acetamide and *d,l-threo*-acetamide	297 g (1.36 moles)
Potassium t-butoxide (95%)	354 g (2.996 moles)
Toluene	8.92 L
Water	1.49 + 0.74 + 3.00 L
Conc. HCl	0.59 + 0.30 L
50% NaOH	0.36 L

Procedure:

A mixture of *d,l-erythro*-acetamide and *d,l-threo*-acetamide (from Example 2.C), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (1.49L). Conc. HCl (0.59L) was added to this resulting mixture, which was stirred for 0.5h. The layers were separated, and the top organic layer was then washed with a prepared solution of conc. HCl (0.30L) and water (0.74L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12 whereby the free base

precipitated out. The crystals were filtered, washed with water (3.00 L), and dried to give 253 g (85%) of *d,l-threo*-α-phenyl-α-piperidyl-(2)-acetamide.

E. *d-threo*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

d,l-threo-α-phenyl-α-piperidyl-(2)- acetamide	253 g (1. 159 moles)
Dibenzoyl-D-tartaric acid	415 g (1. 159 moles)
Isopropanol	8.11 L
6N HCl (aqueous)	1.67 L
Water	1.0 L
Solid NaCl	290g
50% NaOH (aqueous)	1.0 L

Procedure:

Dibenzoyl-D-tartaric acid and *d,l-threo*-α-phenyl-α-piperidyl-(2)-acetamide (from Example 2.D) were dissolved in isopropanol by warming the reaction mixture to ~ 50°C. The resulting clear solution was stirred at ambient temperature for 16h, whereby the tartrate salt of *d-threo*-acetamide crystallized out. The crystals were filtered, and the filter cake was washed with isopropanol and dried in a vacuum oven at 40°C. This tartrate salt was added in portions to a stirred solution of 6N aq. HCl, and the resultant slurry was stirred at ambient temperature for 4h. The slurry was filtered, and the filter cake (containing free dibenzoyl-D-tartaric acid) was washed with water. Solid NaCl was added to the filtrate (which contained *d-threo*-acetamide hydrochloride salt) and the mixture was cooled to ~10°C. The NaOH was added to this mixture to a pH of 12, whereby the free base of *d-threo*-acetamide precipitated out. The precipitated crystals were filtered, washed with water and dried to give 101 g (40%) of *d-threo*-α-phenyl-α-piperidyl-(2)- acetamide.

F. *d-threo*-Methylphenidate Hydrochloride

Materials:

d-threo-α-phenyl-α-piperidyl-(2)- acetamide	101 g (0.46 moles)
Conc. H_2SO_4	121 mL
Methanol	1.1 L
Water	0.81 L
50% NaOH	175 mL
Diethyl ether	1.0 + 1.0 + 1.0 + 1.0 L
Magnesium sulfate	20 g
HCl gas	As needed.

Procedure:

A solution of *d-threo*-α-phenyl-α-piperidyl-(2)- acetamide (from Example 2.E) and conc. H_2SO_4 in methanol was heated to reflux and stirred for 2 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (0.81 L) and ether (1.0 L) were added to the residue. The NaOH was added to a pH of 12, and the layers were separated. The aqueous layer was extracted with ether (1.0 L). $MgSO_4$ was added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas was passed through the filtrate with stirring, whereby white crystals of *d-threo*-methylphenidate hydrochloride precipitated out. The crystals were filtered, washed with ether (1.0 L), and dried to give 100 g (80%) of *d-threo*-methylphenidate hydrochloride.

In contrast to Example 1, the overall yield for Example 2 was 24.5%, an increase of over 66%.

Example 3

Preparation of *l-Threo*-methylphenidate Hydrochloride *Via* Epimerization and Resolution of *d,l-Threo*-amide Enantiomers

A. α-Phenyl-α-pyridyl-2-acetonitrile

Materials:

2-Chloropyridine (99%)	172 g (1.50 moles)
Benzyl cyanide (98%)	188 g (1.576 moles)
Sodium amide (90%)	130 g (3.00 moles)
Toluene	0.59 + 0.10 L
Water	0.52 L
Ethyl acetate	0.26 L
Hexanes	0.94 + 1.17 L
Brine	0.26 L

Procedure:

The reactor was charged with 2-chloropyridine, benzyl cyanide, and toluene (0.59 L). Sodium amide powder was added over a lh period via a solid-addition funnel, keeping the reaction temperature below 300°C. The reaction mixture was stirred for 16h at ambient temperature. The reaction was cooled to ~ 10°C, and quenched with 0.52 L water. Ethyl acetate (0.26 L) was added to solubilize the precipitated product.

The organic layer was separated and washed once with 0.26 L brine, and solvent was removed from the organic layer on a rotovap. Toluene (0. 10 L), followed by hexanes (0.94 L) were added to the resulting residue. The resulting slurry was filtered, and the filter cake was washed with hexanes (1.17 L), and dried to give 265 g of α-phenyl-α-pyridyl-(2)-acetonitrile as light brown crystals (90% yield based on 2-chloropyridine).

B. α-Phenyl-α-pyridyl-(2)-acetamide

Materials:

α-Phenyl-α-pyridyl-(2)-acetonitrile	264 g (1.362 moles)
Conc. H_2SO_4	0.33 L (6.226 moles)
Water	0.98 L
50% NaOH	0.77 L

Procedure:

The reactor was charged with conc. H_2SO_4, and cooled to ~ 10°C. α-Phenyl-α-pyridyl-(2)-acetonitrile (from Example 3.A) was added portionwise, keeping the temperature below 30°C. The reaction was stirred at ambient temperature for 16h. The reaction mixture then was cooled to 10°C, the water was added, and the NaOH was added to a pH of 12, keeping the temperature below 30°C. The resulting crystals were filtered, the filter cake was washed with water, and dried under vacuum to give 289 g (100%) of α-phenyl-α-pyridyl-(2)-acetamide.

C. *d,l-erythro/threo*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

α-Phenyl-α-pyridyl-(2)-acetamide	289 g (1.365 moles)
Platinum oxide (PtO_2)	4.84 g
Acetic acid	1.01 + 2.48 L
Celite	300 + 150 g
Water	2.48 + 0.62 + 1.24 L
50% NaOH	0.33 L

Procedure:

The reactor was charged with α-phenyl-α-pyridyl-(2)-acetamide (from Example 3.B), acetic acid (1.01 L), and PtO_2. The reactor then was filled with hydrogen gas, pressurized to 60 psi, and the mixture hydrogenated at room temperature for 16h. The reaction mixture then was filtered through a pad of Celite (300 g) to remove the catalyst, and the Celite pad is washed with acetic acid (2.48 L). The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in water (2.48 L), filtered through a pad of Celite (150 g), and the Celite pad was washed with water (0.62 L). The resulting filtrate was cooled to 10°C, followed by addition of 50% NaOH until the pH of the mixture was 13 and the free amine crystallized out. The crystals were filtered, washed with water (1.24 L), and dried to give 297 g (100%) of a 4:1 mixture of *d,l-*

erythro-α-phenyl-α-piperidyl-(2)-acetamide and *d,l-threo*-α-phenyl-α-piperidyl-(2)-acetamide.

D. *d,l-threo*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

Mixture of *d,l-erythro*-acetamide and *d,l-threo*-acetamide	297 g (1.36 moles)
Potassium t-butoxide (95%)	354 g (2.996 moles)
Toluene	8.92 L
Water	1.49 + 0.74 + 3.00 L
Conc. HCl	0.59 + 0.30 L
50% NaOH	0.36 L

Procedure:

A mixture of *d,l-erythro*-acetamide and *d,l-threo*-acetamide (from Example 3.C), potassium t-butoxide, and toluene was heated to 70°C and stirred for 16h. The reaction mixture was cooled to room temperature, followed by slow addition of water (1.49L). Conc. HCl (0.59L) was added to this resulting mixture, which was stirred for 0.5h. The layers were separated, and the top organic layer was then washed with a prepared solution of conc. HCl (0.30L) and water (0.74L). The combined aqueous layers were cooled to 10°C, and 50% NaOH was added to a pH of 12 whereby the free base precipitated out. The crystals were filtered, washed with water (3.00 L), and dried to give 253 g (85%) of *d,l-threo*-α-phenyl-α-piperidyl-(2)-acetamide.

E. *l-threo*-α-Phenyl-α-piperidyl-(2)-acetamide

Materials:

d,l-threo-α-phenyl-α-piperidyl-(2)- acetamide	253 g (1. 159 moles)
Dibenzoyl-L-tartaric acid	415 g (1. 159 moles)
Isopropanol	8.11 L
6N HCl (aqueous)	1.67 L
Water	1.0 L
Solid NaCl	290g
50% NaOH (aqueous)	1.0 L

Procedure:

Dibenzoyl-L-tartaric acid and *d,l-threo*-α-phenyl-α-piperidyl-(2)-acetamide (from Example 3.D) is dissolved in isopropanol by warming the reaction mixture to ~ 50°C. The resulting clear solution is stirred at ambient temperature for 16h, whereby the tartrate salt of *l-threo*-acetamide crystallizes out. The crystals are filtered, and the filter cake washed with isopropanol and dried in a vacuum oven at 40°C. This tartrate salt is added in portions to a stirred solution of 6N aq. HCl, and the resultant slurry is stirred at ambient temperature for 4h. The slurry is filtered, and the filter cake (containing free dibenzoyl-L-tartaric acid) is washed with water. Solid NaCl is added to the filtrate (which contains *l-threo*-acetamide hydrochloride salt) and the mixture is cooled to ~10°C. The NaOH is added to this mixture to a pH of 12, whereby the free base of *l-threo*-acetamide precipitates out. The precipitated crystals are filtered, washed with water and dried to give *l-threo*-α-phenyl-α-piperidyl-(2)- acetamide.

F. *l-threo*-Methylphenidate Hydrochloride

Materials:

l-threo-α-phenyl-α-piperidyl-(2)- acetamide	101 g (0.46 moles)
Conc. H_2SO_4	121 mL
Methanol	1.1 L
Water	0.81 L
50% NaOH	175 mL
Diethyl ether	1.0 + 1.0 + 1.0 + 1.0 L
Magnesium sulfate	20 g
HCl gas	As needed.

Procedure:

A solution of *l-threo*-α-phenyl-α-piperidyl-(2)- acetamide (from Example 3.E) and conc. H_2SO_4 in methanol is heated to reflux and stirred for 2 days. The reaction mixture is cooled to room temperature and concentrated under reduced pressure. Water

(0.81 L) and ether (1.0 L) are added to the residue. The NaOH is added to a pH of 12, and the layers are separated. The aqueous layer is extracted with ether (1.0 L). $MgSO_4$ is added to the combined ether layers, filtered, and washed with ether (1.0 L). HCl gas is passed through the filtrate with stirring, whereby white crystals of *l-threo*--methylphenidate hydrochloride precipitate out. The crystals are filtered, washed with ether (1.0 L), and dried to give *l-threo*-methylphenidate hydrochloride.

Those skilled in the art will appreciate that numerous changes and modifications may be made to the preferred embodiments of the present invention and that such changes and modifications may be made without departing from the spirit of the invention. It is therefore intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.